


# Efficient and Divergent Total Synthesis of (–)-Epicoccin G and (–)-Rostratin A Enabled by Double C(sp<sup>3</sup>)–H Activation

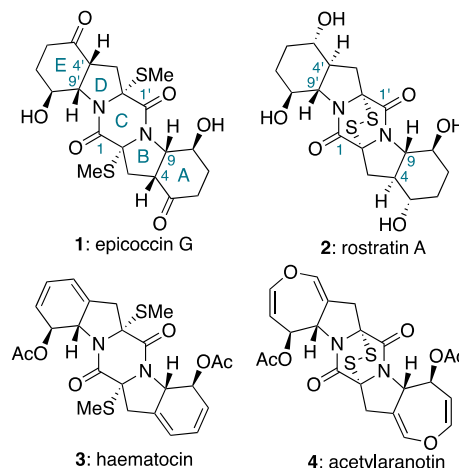
Pierre Thesmar and Olivier Baudoin\*

Department of Chemistry, University of Basel, St. Johannis-Ring 19, CH-4056 Basel, Switzerland

 Supporting Information

**ABSTRACT:** Dithiodiketopiperazines are complex polycyclic natural products possessing a variety of interesting biological activities. Despite their interest, relatively few total syntheses have been completed. We herein report the enantioselective, scalable, and divergent total synthesis of two symmetrical pentacyclic dithiodiketopiperazines, (–)-epiccocin G and (–)-rostratin A. A common intermediate was synthesized on a multigram scale from inexpensive, commercially available starting materials using an enantioselective organocatalytic epoxidation and a double C(sp<sup>3</sup>)–H activation as key steps, with the latter allowing the efficient simultaneous construction of the two five-membered rings. In addition to the *cis,cis*-fused target (–)-epiccocin G, the more challenging (–)-rostratin A, possessing two *trans* ring junctions, was obtained for the first time on a 500 mg scale through the optimization of each step and validation on multigram quantities. Both natural products were synthesized with high overall yields (13–20%). This study should facilitate access to this fascinating and yet understudied family of biologically active natural products.

Dithiodiketopiperazines (DTPs) constitute an abundant class of natural products exhibiting a great diversity of biological properties.<sup>1</sup> In particular, (–)-epiccocin G (**1**), isolated from the fungus *Epicoccum nigrum*, was shown to possess in vitro anti-HIV-1<sup>2</sup> and antiparasitic activities,<sup>3</sup> and (–)-rostratin A (**2**), isolated from the marine-derived fungus *Exserohilum rostratum*, was shown to be cytotoxic against HCT-116 cancer cells (Figure 1).<sup>4</sup> These interesting bioactivities, combined with a challenging sulfurated fused pentacyclic framework, have attracted the attention of synthetic chemists in recent years. However, despite a significant number of synthetic studies,<sup>5</sup> only three research groups have reported total syntheses of DTPs based on such a pentacyclic framework, and hence these molecules remain major synthetic challenges. On one hand, Nicolaou and co-workers reported the pioneering synthesis of several 6-5-6-5-6 DTPs, including epicoccin G (**1**) and haematocin (**3**).<sup>3,6</sup> Shortly after, the groups of Reisman and Tokuyama disclosed the synthesis of the dihydrooxepine-containing 7-5-6-5-7 DTPs acetylaranotin (**4**)<sup>7,8</sup> and acetylpoaranotin.<sup>9</sup> Interestingly, all of these total syntheses proceed with the initial construction of the AB/DE bicyclic systems and assembly of the central DKP ring (C) at a later stage.



**Figure 1.** Examples of naturally occurring dithiodiketopiperazines with a pentacyclic framework.

In recent years, C–H activation has gained increasing importance in total synthesis, offering step-economical access to key intermediates or allowing late-stage introduction of key functional groups.<sup>10</sup> In this context, we and others developed an array of methods based on Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)–H activation for the construction of various carbo- and heterocyclic systems<sup>11</sup> and demonstrated their applicability in natural product synthesis.<sup>12</sup> Herein, we report a new strategy based on double C–H activation for the concise and divergent enantioselective synthesis of (–)-epiccocin G (**1**) and (–)-rostratin A (**2**), which are synthesized for the second and first time, respectively. Structurally, these molecules differ from the oxidation degree at C5/C5', the nature of the sulfur substituents at C2/C2', and last but not least the presence of *cis* (**1**) or *trans* (**2**) A-B/D-E ring junctions.

Our retrosynthetic analysis is depicted in Figure 2. Target compounds **1** and **2** were thought to arise from the common intermediate **5** through manipulation of the C4–C5/C4'–C5' double bonds and late-stage introduction of the sulfur atoms at C2/C2', as advised in earlier studies.<sup>3,6–8</sup> For the synthesis of **2**, we anticipated that the control of the contra-thermodynamic *trans* ring junctions would be a significant challenge. Indeed, the *cis,cis* 6-5-6-5-6 pentacyclic system was calculated to be more stable than the *trans,trans* system by 5 kcal mol<sup>–1</sup> by DFT (Supporting Information, Figure S1), and no such *trans*-

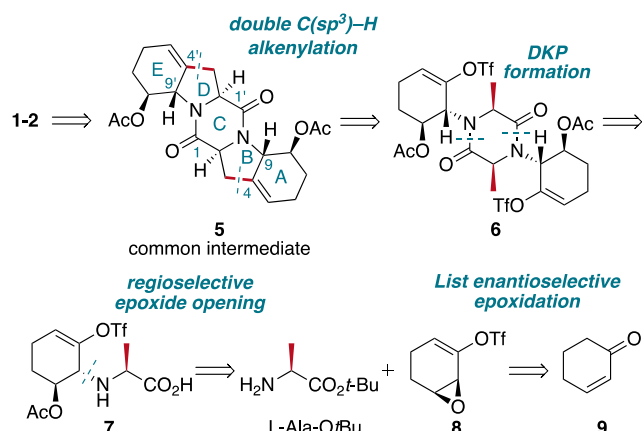


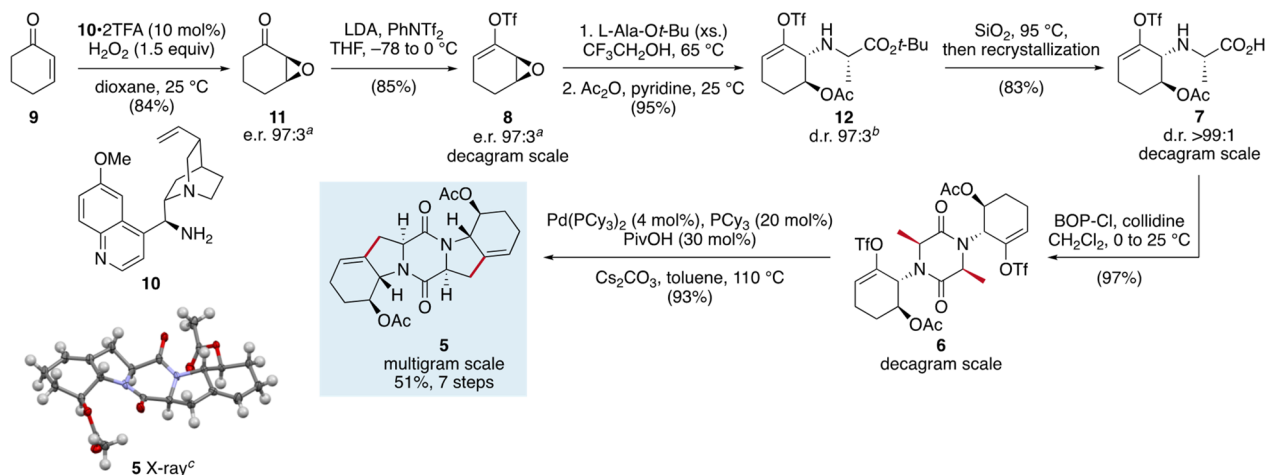
Figure 2. Retrosynthetic analysis.

fused pentacyclic DTP natural product has been synthesized to date, to the best of our knowledge. A twofold application of our C(sp<sup>3</sup>)-H activation transform to the C3-C4 and C3'-C4' bonds in 5 would then lead to the ditriflate precursor 6. The intramolecular C(sp<sup>3</sup>)-H alkenylation of cyclohexenyl bromides<sup>13</sup> and triflates<sup>14</sup> has been reported, but such a double C(sp<sup>3</sup>)-H alkenylation reaction is unprecedented.<sup>15</sup> Diketopiperazine formation by cyclodimerization would allow building intermediate 6 from monomeric amino acid 7. The latter would arise from the regioselective and stereospecific opening of enantiomerically pure epoxide 8 with L-alanine *tert*-butyl ester.<sup>16</sup> Finally, epoxide 8 would be obtained from cyclohexenone 9 by using List's organocatalytic enantioselective epoxidation.<sup>17</sup> This retrosynthetic plan differs from most previous approaches<sup>5,6</sup> by constructing simultaneously rings B and D from A-C-E precursor 6 instead of constructing ring C last,<sup>5d,g</sup> while minimizing nonstrategic functional group manipulations. This should result in a significant overall step-economy for the synthesis of targets 1 and 2.

The enantiopure dialkene intermediate 5 was synthesized in high overall yield from inexpensive starting materials according to the seven-step sequence depicted in Scheme 1. The most effective method to access epoxide 8 was found to be List's asymmetric epoxidation of cyclohexenone 9, catalyzed by

cinchona amine 10 and using aqueous hydrogen peroxide as the oxidant.<sup>17</sup> This method was routinely performed on a decagram scale and provided an excellent yield and enantioselectivity (e.r. 97:3) for keto-epoxide 11. The triflation of 11 was performed via formation of the lithium enolate and reaction with phenyl triflimide to give alkenyl triflate 8, which was sensitive and rapidly engaged in the next step. The epoxide was opened via nucleophilic substitution by an excess of L-alanine *tert*-butyl ester in trifluoroethanol at 65 °C. The ring-opening occurred with complete regioselectivity, consistent to a related example.<sup>16</sup> Of note, 50–60% of the initially engaged L-alanine *tert*-butyl ester could be easily recovered. The secondary alcohol was then acetylated to give compound 12 as a 97:3 diastereoisomeric mixture matching the enantiomeric purity of epoxide 8, as expected from the stereospecificity of the epoxide opening. Cleavage of the *tert*-butyl ester under mildly acidic conditions furnished amino acid 7, which was isolated as a single diastereoisomer after recrystallization (79% overall yield from epoxide 8). Cyclodimerization of 7 mediated by BOP-Cl and collidine furnished the C<sub>2</sub>-symmetric diketopiperazine 6 in high yield on a decagram scale. Bis-triflate 6 was then submitted to the key double C(sp<sup>3</sup>)-H alkenylation reaction. Reaction conditions were optimized, starting with standard conditions that proved successful in previous complex settings (see the Supporting Information for details).<sup>12b,c</sup> In particular, use of the well-defined Pd(PCy<sub>3</sub>)<sub>2</sub> complex (4 mol %), supplemented with free tricyclohexylphosphine (20 mol %), was found to be key to avoid premature catalyst decomposition, leading to unproductive mixtures including 5, unreacted 6, the mono-C-H alkenylation product, and proto-detriflated products. Moreover, epimerization at the DKP ring was observed without additional free ligand when the reaction was carried out at the high concentrations required for upscaling. With this important modification, the double C-H activation occurred in high yield (93%) and in a reproducible manner on multigram quantities (8–9 g of 5 was typically isolated per batch). This contributed to a short and efficient (51% over seven steps) synthesis of intermediate 5, the structure and absolute configuration of which were confirmed by X-ray diffraction analysis.

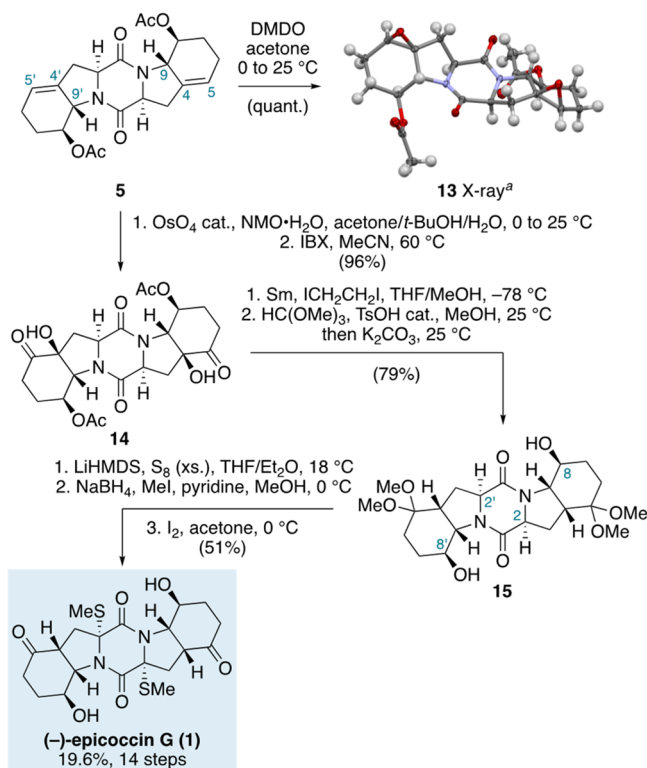
Scheme 1. Seven-Step Synthesis of Intermediate 5



<sup>a</sup>Measured by GC on a chiral stationary phase. <sup>b</sup>Measured by <sup>19</sup>F NMR. <sup>c</sup>Thermal ellipsoids shown at 50% probability. BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

After having secured an efficient access to intermediate **5**, we turned to the synthesis of (–)-epiccocin G (Scheme 2). Initial

### Scheme 2. Synthesis of (–)-Epiccocin G



<sup>a</sup>Thermal ellipsoids shown at 50% probability. DMDO = dimethyldioxirane; NMO = *N*-methylmorpholine *N*-oxide; IBX = 2-iodoxybenzoic acid; LiHMDS = lithium bis(trimethylsilyl)amide.

attempts to perform the hydroboration/oxidation of the C4–C5/C4'–C5' alkenes with various boranes were met with little success. In contrast, epoxidation occurred with high efficiency when DMDO was used, leading to the bis-epoxide **13** with complete *cis* diastereoselectivity with respect to the angular C9/C9' hydrogens, as confirmed by X-ray diffraction analysis. However, attempts at regioselective ring-opening of these epoxides in the presence of various Lewis or Brønsted acids failed to provide useful synthetic intermediates.

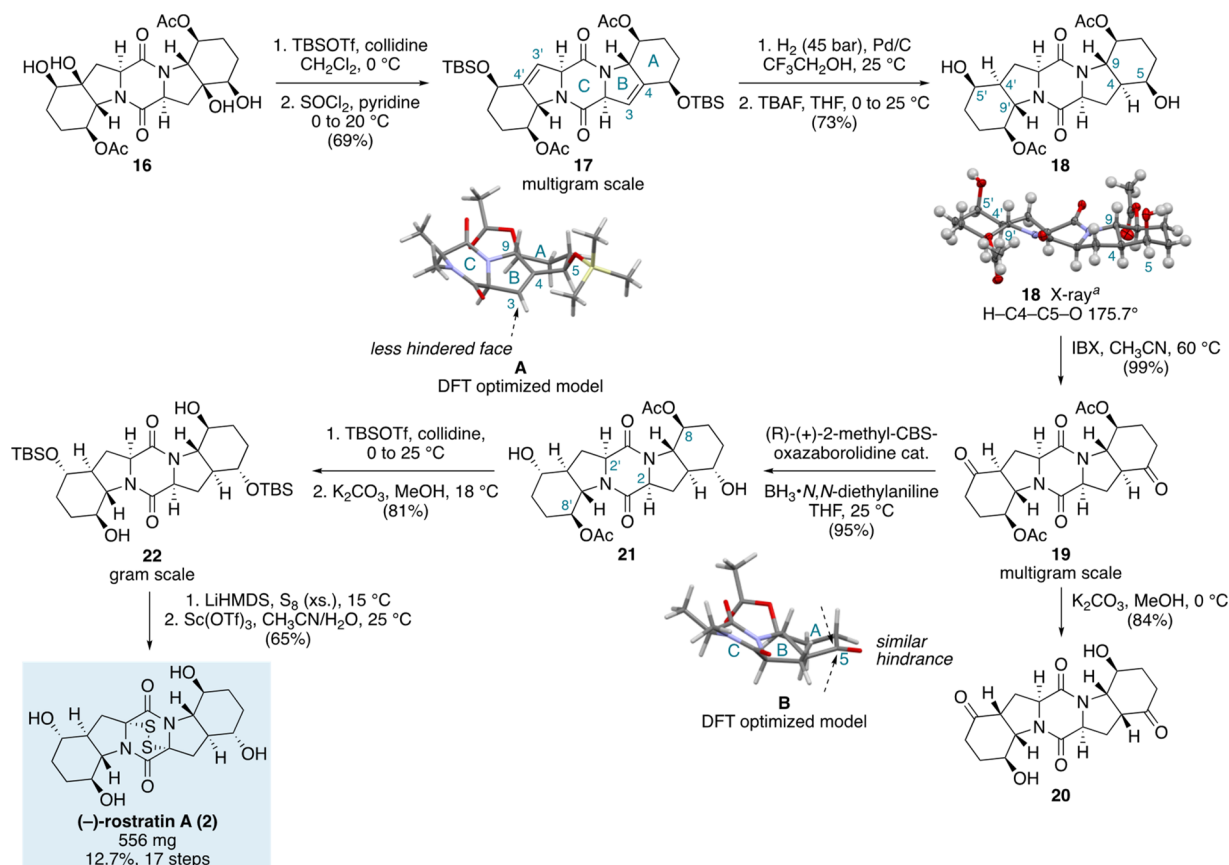
The best option was to perform an Upjohn dihydroxylation, which likewise occurred with complete *cis* diastereoselectivity, followed by oxidation of the secondary alcohols at C5/C5' with IBX, which gave bis- $\alpha$ -hydroxyketone **14** in excellent yield (96% for two steps). Samarium(II) iodide-mediated reduction of these hydroxyketones<sup>18</sup> then led to the thermodynamically favored *cis,cis*-fused diketone, which was protected as a dimethoxyketal and deacetylated in a one-pot fashion (**15**). The next important step was the introduction of the C2/C2' thiomethyl groups, which was performed under conditions adapted from Nicolaou and co-workers.<sup>3,6</sup> However, whereas the latter obtained a 1.4:1 mixture of *cis* diastereoisomers epimeric at both C2 and C2' from a different precursor, the thiolation of **15** occurred with a high diastereoselectivity in favor of the desired C2 $_{\alpha}$ /C2' $_{\alpha}$  diastereoisomer. This behavior could arise from a directing effect of the C8 and C8' hydroxy groups, which according to molecular models are spatially close to the C2' and C2 positions, respectively, and which were not present at the sulfuration stage in the Nicolaou synthesis.

Finally, iodine-mediated cleavage<sup>19</sup> of the C5/C5' ketals led to epiccocin G (**1**) in 51% yield for three steps. Overall, (–)-epiccocin G (23 mg) was synthesized in 19.6% yield over 14 steps from cyclohexenone **9**, which represents a major improvement compared to the first synthesis (1.5% over 17 steps).<sup>3,6</sup>

We then set out to explore the synthesis of (–)-rostratin A (Scheme 3). Different strategies were considered to install the challenging *trans,trans* ring junctions. In particular, attempts at performing directed hydrogenations of C3–C4/C3'–C4' double bonds from allylic C5 $_{\alpha}$ /C5' $_{\alpha}$  or C2 $_{\alpha}$ /C2' $_{\alpha}$  hydroxy groups failed to provide the desired relative configuration. These failures led us to consider a sterically controlled hydrogenation of C3–C4/C3'–C4' alkenes using C5 $_{\beta}$ /C5' $_{\beta}$ -protected hydroxy groups. To this purpose, tetraol **16**, obtained from the above-mentioned Upjohn dihydroxylation of intermediate **5**, was protected as a bis-silyl ether, and SOCl<sub>2</sub>-mediated dehydration furnished dialkene **17** in good yield on a multigram scale.

The examination of the DFT-optimized structure of an A-B-C truncated model **A** indicated that the  $\beta$  face of the C3–C4/C3'–C4' alkenes should be efficiently shielded by the silyloxy groups. Consistent with this analysis, the hydrogenation of **17** led to the desired *trans,trans*-fused product, as determined by NOESY NMR. TBAF-mediated deprotection provided diol **18**, the *trans,trans* configuration of which was confirmed by X-ray diffraction analysis. At this stage, attempts to invert the configuration of the C5/C5' alcohols by Mitsunobu or related reactions failed, due to the propensity of compound **18** to undergo dehydration, regenerating the C4–C5/C4'–C5' double bonds. Indeed, the X-ray structure of **18** shows that the C5OH and C5'OH groups lie at axial positions of the chairlike rings A and E with a mean dihedral angle H–C4(C4')–C5(C5')–O of 175.7°, hence almost perfectly aligned for *anti*-elimination. To solve this problem, we turned to an oxidation–reduction strategy. IBX-mediated oxidation of diol **18** led to diketone **19**, which easily epimerized at C4/C4' in the presence of acids or bases to give the thermodynamic *cis,cis* diastereoisomer, as shown with the formation of **20** upon transesterification from **19**. The truncated DFT-optimized model **B** showed no particular steric preference for the reduction of the C5 ketone in favor of the C5 $_{\alpha}$  alcohol, and indeed attempts at reducing diketone **19** with standard achiral reagents furnished unproductive diastereomeric mixtures. Consequently, we turned to the use of a reagent-based stereochemical control and found that the use of catalytic (R)-(+)-2-methyl-CBS-oxazaborolidine in combination with the borane-2,6-diethylaniline complex, conditions well adapted to aliphatic ketones,<sup>20</sup> afforded the desired C5 $_{\alpha}$ /C5' $_{\alpha}$  diol **21** exclusively and without epimerization at C4/C4'. The cleavage of the C8/C8' acetates led to the corresponding tetraol, but the latter was found to be insoluble in usual aprotic solvents required for the subsequent step. Overcoming this additional problem required a more indirect strategy. TBS diprotection and acetate cleavage afforded a less polar diol **22**, which was submitted to sulfuration with LiHMDS and S<sub>8</sub> as above for **15** in the synthesis of epiccocin G. However, in contrast to **15**, which provided a mixture of C2/C2' epipolysulfides as reported by Nicolaou and co-workers,<sup>3,6</sup> the desired 2,2'-epidissulfide was the major product of the sulfuration of the TBS-protected diol **22**. This fortunate result suppressed the need for an additional reduction/reoxidation sequence, which would have been otherwise necessary.

### Scheme 3. Synthesis of (–)-Rostratin A



<sup>a</sup>Thermal ellipsoids shown at 50% probability. TBS = *tert*-butyldimethylsilyl; TBAF = *n*-Bu<sub>4</sub>NF.

In addition, similar to epicoccin G, the sulfuration of **22** occurred with exclusive C2<sub>α</sub>/C2'α diastereoselectivity. Finally, the scandium triflate-mediated<sup>21</sup> mild cleavage of the TBS groups directly provided (–)-rostratin A (**2**), the physical properties of which matched the reported data.<sup>4</sup> Rostratin A was synthesized for the first time in 12.7% yield over 17 steps. This synthetic sequence was reproducible and scalable, allowing to obtain 556 mg of synthetic rostratin A.

In conclusion, we successfully achieved the enantioselective total synthesis of the natural dithiodiketopiperazines (–)-epicoccin G and (–)-rostratin A in 14 and 17 steps, respectively, and with high overall yields from inexpensive starting materials. The common precursor to both target molecules was readily synthesized using an enantioselective organocatalytic epoxidation and a double C(sp<sup>3</sup>)–H activation as key steps. The most challenging target, rostratin A, possessing two *trans* ring junctions, was synthesized for the first time on a 500 mg scale thanks to a careful analysis of steric features and through a combination of substrate- and reagent-based stereochemical control. This study further demonstrates the power of C–H activation to, combined with more established methods, streamline the access to complex biologically active natural products.

### ■ ASSOCIATED CONTENT

Experimental procedures; spectral and characterization data for all compounds (PDF)

X-ray diffraction data for **5** (CIF)

X-ray diffraction data for **13** (CIF)

X-ray diffraction data for **18** (CIF)

Coordinate files for computational modeling (XYZ)

### ■ AUTHOR INFORMATION

#### Corresponding Author

\*[olivier.baudoin@unibas.ch](mailto:olivier.baudoin@unibas.ch)

#### ORCID

Olivier Baudoin: 0000-0002-0847-8493

#### Notes

The authors declare no competing financial interest.

### ■ ACKNOWLEDGMENTS

This work was financially supported by the University of Basel. We thank Brian Freudiger and Philipp Meyer for preparative work, Dr. Markus Neuburger and Dr. Alessandro Prescimone for X-ray diffraction analyses, Dr. Daniel Häussinger for assistance with NMR experiments, and Dr. Michael Pfeffer for MS analyses. We also thank Prof. Benjamin List for helpful advices on the enantioselective epoxidation.

### ■ REFERENCES

- (1) Borthwick, A. D. 2,5-Diketopiperazines: synthesis, reactions, medicinal chemistry, and bioactive natural products. *Chem. Rev.* **2012**, *112*, 3641–3716.



- (2) (a) Guo, H.; Sun, B.; Gao, H.; Chen, X.; Liu, S.; Yao, X.; Liu, X.; Che, Y. Diketopiperazines from the *Cordyceps*-Colonizing Fungus *Epicoccum nigrum*. *J. Nat. Prod.* **2009**, *72*, 2115–2119. (b) Wang, J.-M.; Ding, G.-Z.; Fang, L.; Dai, J.-G.; Yu, S.-S.; Wang, Y.-H.; Chen, X.-G.; Ma, S.-G.; Qu, J.; Xu, S.; Du, D. Thiodiketopiperazines produced by the endophytic fungus *Epicoccum nigrum*. *J. Nat. Prod.* **2010**, *73*, 1240–1249.
- (3) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smees, D. F.; Day, C. W.; Bopp, S.; Winzler, E. A. Synthesis and biological evaluation of epidithio-, epitetrahydro-, and bis-(methylthio)-diketopiperazines: synthetic methodology, enantioselective total synthesis of epicoccin G, 8,8'-epi-ent-rostratin B, gliotoxin, gliotoxin G, emethallicin E, and haematocin and discovery of new antiviral and antimalarial agents. *J. Am. Chem. Soc.* **2012**, *134*, 17320–17332.
- (4) Tan, R. X.; Jensen, P. R.; Williams, P. G.; Fenical, W. Isolation and structure assignments of rostratins A–D, cytotoxic disulfides produced by the marine-derived fungus *Exserohilum rostratum*. *J. Nat. Prod.* **2004**, *67*, 1374–1382.
- (5) (a) Middleton, M. D.; Peppers, B. P.; Diver, S. T. Studies directed toward the synthesis of the scabrosins: validation of a tandem enyne metathesis approach. *Tetrahedron* **2006**, *62*, 10528–10540. (b) Gross, U.; Nieger, M.; Bräse, S. Stereoselective synthesis of the epicoccin core. *Org. Lett.* **2009**, *11*, 4740–4742. (c) Gross, U.; Nieger, M.; Bräse, S. A unified strategy targeting the thiodiketopiperazine mycotoxins exserohilone, gliotoxin, the epicoccins, the epicorazines, rostratin A and aranotin. *Chem. - Eur. J.* **2010**, *16*, 11624–11631. (d) Zipfel, H. F.; Carreira, E. M. An efficient synthesis strategy to the core structure of 6–5–6–5–6-membered epipolythiodiketopiperazines. *Org. Lett.* **2014**, *16*, 2854–2857. (e) Belov, D. S.; Ratmanova, N. K.; Andreev, I. A.; Kurkin, A. V. Synthesis of bicyclic proline derivatives by the aza-Cope-Mannich reaction: formal synthesis of (±)-acetylaranotin. *Chem. - Eur. J.* **2015**, *21*, 4141–4147. (f) Zhong, S.; Sauter, P. F.; Nieger, M.; Bräse, S. Stereoselective synthesis of highly functionalized hydroindoles as building blocks for rostratins B–D and synthesis of the pentacyclic core of rostratin C. *Chem. - Eur. J.* **2015**, *21*, 11219–11225. (g) Zipfel, H. F.; Carreira, E. M. A unified strategy to 6–5–6–5–6-membered epipolythiodiketopiperazines: studies towards the total synthesis of scabrosin diacetate and haematocin. *Chem. - Eur. J.* **2015**, *21*, 12475–12480.
- (6) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. Total synthesis of epicoccin G. *J. Am. Chem. Soc.* **2011**, *133*, 8150–8153.
- (7) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. Enantioselective total synthesis of (–)-acetylaranotin, a dihydrooxepine epidithiodiketopiperazine. *J. Am. Chem. Soc.* **2012**, *134*, 1930–1933.
- (8) Fujiwara, H.; Kurogi, T.; Okaya, S.; Okano, K.; Tokuyama, H. Total synthesis of (–)-acetylaranotin. *Angew. Chem., Int. Ed.* **2012**, *51*, 13062–13065.
- (9) Wang, H.; Regan, C. J.; Codelli, J. A.; Romanato, P.; Puchlopek-Dermenci, A. L. A.; Reisman, S. E. Enantioselective synthesis of (–)-acetylapanotin. *Org. Lett.* **2017**, *19*, 1698–1701.
- (10) (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C–H bond functionalization: emerging synthetic tools for natural products and pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960–9009. (b) Chen, D. Y.-K.; Youn, S. W. C–H activation: a complementary tool in the total synthesis of complex natural products. *Chem. - Eur. J.* **2012**, *18*, 9452–9474. (c) Karimov, R. R.; Hartwig, J. F. Transition-metal-catalyzed selective functionalization of C(sp<sup>3</sup>)–H bonds in natural products. *Angew. Chem., Int. Ed.* **2018**, *57*, 4234–4241. (d) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. Recent applications of C–H functionalization in complex natural product synthesis. *Chem. Soc. Rev.* **2018**, *47*, 8925–8967. (e) Dailier, D.; Danoun, G.; Baudoin, O. Applications of catalytic organometallic C(sp<sup>3</sup>)–H bond functionalization. *Top. Organomet. Chem.* **2015**, *56*, 133–154. (f) Brady, P. B.; Bhat, V. Recent applications of Rh- and Pd-catalyzed C(sp<sup>3</sup>)–H functionalization in natural product total synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 5179–5190.
- (11) Baudoin, O. Ring construction by palladium(0)-catalyzed C(sp<sup>3</sup>)–H activation. *Acc. Chem. Res.* **2017**, *50*, 1114–1123.
- (12) (a) Chaumontet, M.; Piccardi, R.; Baudoin, O. Synthesis of 3,4-dihydroisoquinolines by a C(sp<sup>3</sup>)–H activation/electrocyclization strategy: total synthesis of coralydine. *Angew. Chem., Int. Ed.* **2009**, *48*, 179–182. (b) Dailier, D.; Danoun, G.; Baudoin, O. A general and scalable synthesis of aeruginosin marine natural products based on two strategic C(sp<sup>3</sup>)–H activation reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 4919–4922. (c) Dailier, D.; Danoun, G.; Ourri, B.; Baudoin, O. Divergent synthesis of aeruginosins based on a C(sp<sup>3</sup>)–H activation strategy. *Chem. - Eur. J.* **2015**, *21*, 9370–9379. (d) Melot, R.; Craveiro, M. V.; Bürgi, T.; Baudoin, O. Divergent enantioselective synthesis of (nor)illudalane sesquiterpenes via Pd<sup>0</sup>-catalyzed asymmetric C(sp<sup>3</sup>)–H activation. *Org. Lett.* **2019**, *21*, 812–815. (e) Melot, R.; Craveiro, M. V.; Baudoin, O. Total synthesis of (nor)illudalane sesquiterpenes based on a C(sp<sup>3</sup>)–H activation strategy. *J. Org. Chem.* **2019**, DOI: 10.1021/acs.joc.9b01669.
- (13) Sofack-Kreutzer, J.; Martin, N.; Renaudat, A.; Jazzar, R.; Baudoin, O. Synthesis of hexahydroindoles by intramolecular C<sub>sp3</sub>–H alkenylation: application to the synthesis of the core of aeruginosins. *Angew. Chem., Int. Ed.* **2012**, *51*, 10399–10402.
- (14) Suetsugu, S.; Muto, N.; Horinouchi, M.; Tsukano, C.; Takemoto, Y. Synthesis and application of tetrahydro-2H-fluorenes by a Pd(0)-catalyzed benzylic C(sp<sup>3</sup>)–H functionalization. *Chem. - Eur. J.* **2016**, *22*, 8059–8062.
- (15) (a) Pierre, C.; Baudoin, O. Synthesis of polycyclic molecules by double C(sp<sup>2</sup>)–H/C(sp<sup>3</sup>)–H arylations with a single palladium catalyst. *Org. Lett.* **2011**, *13*, 1816–1819. (b) Rocaboy, R.; Dailier, D.; Baudoin, O. A four-step synthesis of (±)-γ-lycorane via Pd<sup>0</sup>-catalyzed double C(sp<sup>2</sup>)–H/C(sp<sup>3</sup>)–H arylation. *Org. Lett.* **2018**, *20*, 772–775.
- (16) Ebrahimian, G. R.; Mollat du Jourdin, X.; Fuchs, P. L. Jacobsen protocols for large-scale epoxidation of cyclic dienyl sulfones: application to the (+)-pretazettine core. *Org. Lett.* **2012**, *14*, 2630–2633.
- (17) (a) Wang, X.; Reisinger, C. M.; List, B. Catalytic asymmetric epoxidation of cyclic enones. *J. Am. Chem. Soc.* **2008**, *130*, 6070–6071. (b) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. The cinchona primary amine-catalyzed asymmetric epoxidation and hydroperoxidation of α,β-unsaturated carbonyl compounds with hydrogen peroxide. *J. Am. Chem. Soc.* **2013**, *135*, 6677–6693.
- (18) Molander, G. A.; Hahn, G. Lanthanides in organic synthesis. 2. Reduction of α-heterosubstituted ketones. *J. Org. Chem.* **1986**, *51*, 1135–1138.
- (19) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. Highly efficient chemoselective deprotection of O,O-acetals and O,O-ketals catalyzed by molecular iodine in acetone. *J. Org. Chem.* **2004**, *69*, 8932–8934.
- (20) Salunkhe, A. M.; Burkhardt, E. R. Highly enantioselective reduction of prochiral ketones with N,N-diethylaniline•borane (DEANB) in oxazaborolidine-catalyzed reductions. *Tetrahedron Lett.* **1997**, *38*, 1523–1526.
- (21) Oriyama, T.; Kobayashi, Y.; Noda, K. Chemoselective and practical deprotection of alkyl trialkylsilyl ethers in the presence of aryl trialkylsilyl ethers by a catalytic amount of Sc(OTf)<sub>3</sub>. *Synlett* **1998**, *1998*, 1047–1048.